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PREPARATION OF α-KETO ESTER ENOL ACETATES AS POTENTIAL PRODRUGS OF HUMAN NEUTROPHIL ELASTASE INHIBITORS

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Abstract: Enol acetates of a-keto esters with *E* configuration were prepared as potential prodrugs for human neutrophil elastase (HNE) inhibitors.

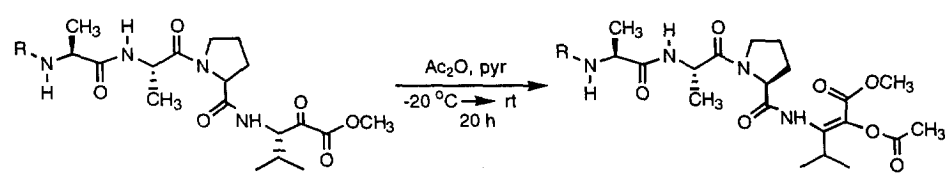
We recently described a series of tripeptidyl pentafluoroethyl ketones as potent, orally active inhibitors of human neutrophil elastase (HNE).[1] In a subsequent report, we showed that enol ester derivatives of these pentafluoroethyl ketones were effective prodrugs.[2] Cleavage of these prodrugs with esterase efficiently converted them to the parent pentafluoroethyl ketones. In addition to simplifying the parent drug by eliminating a diastereomeric center, these enol ester prodrugs provided a drug delivery system which sustained or increased the oral bioavailability of the parent drug.

Substrate-based α-keto esters have also been shown by us[3] and others[4,5] to be potent inhibitors of both serine (including HNE) and cysteine proteinases. Since α-keto esters are more versatile proteinase inhibitors than are fluorinated ketones, which in general are inhibitors of serine proteinases but not of cysteine proteinases,[6-8] we wished to extend the enol ester concept to α-keto esters. In this report is described the preparation of enol acetates of α-keto esters with *E* configuration that serve as potential prodrugs for HNE inhibitors.

The syntheses[9] of the α-keto ester enol acetate prodrugs **2** and **4** are shown in Scheme 1. To demonstrate the concept with this class of inhibitor, we chose two peptidyl α-keto esters whose syntheses and enzyme inhibition properties we have previously described.[1,3d,10]

In Table 1 are shown rates of HNE substrate hydrolysis in the presence of enol acetates **2** and **4**, under different assay conditions. In the absence of esterase, the rates for substrate hydrolysis were depressed by **2** and **4**, relative to control under the specified assay conditions. When esterase was present, inhibition of substrate hydrolysis was substantial and the K_i values determined for **2** and **4** under these conditions were 130 nM

Scheme I



1 R = 4-ClC$_6$H$_4$SO$_2$NHCOC$_6$H-4-CO-
3 R = CH$_3$OCOCH$_2$CH$_2$CO-

2 R = 4-ClC$_6$H$_4$SO$_2$NHCOC$_6$H-4-CO-
4 R = CH$_3$OCOCH$_2$CH$_2$CO-

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Table 1. Rate of Substrate[a] Hydrolysis by Human Neutrophil Elastase

Compound	Rate (%)[b]	K_i (nM)[c]
control	100	—
4 (1 μM)	81[d]	—
4 (9 μM)	35[d]	—
4 (1 μM) with esterase[e]	24[d]	130
4 (9 μM) with esterase[e]	2.8[d]	130
3	—	200
2 (10 nM)	99[f]	—
2 (45 nM)	94[f]	—
2 (10 nM) with esterase[e]	76[f]	13
2 (45 nM) with esterase[e]	37[f]	13
1	—	2

[a]Substrate used was MeO-Suc-Ala-Ala-Pro-Val-*p*-nitroanilide. At a substrate concentration of 0.20 mM, $K_m = 0.16$ mM. [b]Rate without inhibitor was defined as 100%. [c]K_i values were determined as described in reference 3a. [d]Average of 3 runs. [e]Porcine kidney esterase (Sigma). [f]Average of 2 runs.

and 13 nM, respectively. These K_i values were similar to those determined for the parent inhibitors **1** and **3** (200 nM and 2 nM, respectively).

In summary, we have described the syntheses of α-keto ester enol acetates and provided good evidence that they act as prodrugs, in the presence of esterase, for their parent α-keto ester HNE inhibitors.

References and Notes

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8. There is at least one reported exception to this general rule. An α,α-difluoro-β-dicarbonyl substrate-based inhibitor of IL-1β converting enzyme has been described. See Robinson, R. P.; Donahue, K. M. *J. Org. Chem.* **1992**, *57*, 7309.
9. To stirring pyridine (1.25 ml) under an inert atmosphere at -20 °C was added **1** (156 mg, 0.30 mmol) followed by acetic anhydride (0.29 ml, 3.0 mmol). The reaction mixture was allowed to warm to room temperature. After stirring for 20 h, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with 0.3N HCl (2 x 20 mL) and brine (15 mL). The CH_2Cl_2 was dried ($MgSO_4$) and concentrated to give crude product which was purified by flash chromatography (silica gel, 4 x 14 cm column). Elution with a 1:3 to 1:1 acetone:EtOAc gradient gave 88 mg (53%) of enol ester **2** as a colorless oil, as a 9:1 mixture of *E*:*Z* isomers. For compound **2**: ^{1}H NMR ($CDCl_3$, 400 MHz, *E*-isomer signals) δ 10.16 (br s, 1H, CONHC=C), 7.17 (br d, 1H, NH), 6.43 (br d, 1H, NH), 4.81-4.72 (m, 1H, Ala CH), 4.58-4.48 (m, 2H, Ala CH and Pro CH), 3.76-3.63 (m, 2H, CH_2N), 3.68 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 2.68-2.60 and 2.53-2.45 (pr m, 4H, $COCH_2CH_2CO$), 2.22-1.95 (m, 4H, $NCH_2CH_2CH_2$), 2.20 (s, 3H, $COCH_3$), 1.37 (d, J = 2.7 Hz, 3H, Ala CH_3) 1,32 (d, J = 2.7 Hz, 3H, Ala CH_3), 1.14 and 1.13 (pr d, J = 5.4 Hz, 6H, Val CH_3 groups); MS (CI/CH_4) *m/z* (rel intensity) 555 ($M + H^+$, 62), 354 (38), 299 (100); HRMS $C_{25}H_{39}N_4O_{10}$ (MH^+) calcd 555.2666; found 555.2665. Compound **4** was prepared using the same procedure in 16% yield. Spectral data were consistent with structure and confirmed the presence, in the purified sample, of only the *E*-isomer.
10. A recent article describes a modified Dakin-West Procedure for related enol esters of α-keto esters. See Li, Z.; Ortega-Vilain, A.; Patel, G.S.; Chu, D.; Foreman, J. E.; Eveleth, D. D.; Powers, J.C. *J. Med. Chem.* **1996**, *39*, 4089.